Regional Cerebral Blood Flow Utilizing the Gamma Camera and Xenon Inhalation: Reproducibility and Clinical Applications


SUMMARY A modified collimator and standard gamma camera have been used to measure regional cerebral blood flow following inhalation of radioactive xenon. The collimator and a simplified analysis technique enables excellent statistical accuracy to be achieved with acceptable precision in the measurement of grey matter blood flow. The validity of the analysis was supported by computer modelling and patient measurements.

Sixty-one patients with subarachnoid haemorrhage, cerebrovascular disease or dementia were retested to determine the reproducibility of our method. The measured coefficient of variation was 6.5%.

Of forty-six patients who had a proven subarachnoid haemorrhage, 15 subsequently developed cerebral ischaemia. These showed a CBF of 42 ± 6 ml·minute⁻¹·100 g brain⁻¹ compared with 49 ± 11 ml·minute⁻¹·100 g brain⁻¹ for the remainder. There is evidence that decreasing blood flow and low initial flow correlate with the subsequent onset of cerebral ischaemia.

Since the early work of Mallet and Veall1 and later Obrist et al.2,3 to measure regional cerebral blood flow atraumatically, most investigators have used multiple radiation detectors placed strategically over the cranium. As an alternative to multiple detectors, the gamma camera has been used successfully following an intercarotid injection of xenon.4,5 However, attempts to use the gamma camera in combination with xenon inhalation have not been widely accepted.6

There clearly would be great benefit for routine hospital medicine if a technique could be developed to use the gamma camera with xenon inhalation. For this reason, we have introduced a modified collimator to improve counting statistics whilst still retaining the ability to measure regional blood flow. This has been combined with a simplified analysis technique7 which further improves the statistical accuracy of the analysis, and requires a shorter patient examination period.

The validity of this approach has been tested using computer modelling and patient measurements to show the accuracy and reproducibility of the results. The data show that the technique is reproducible and clinically useful.

Method

Collimator Design

The standard gamma camera collimator is designed for high resolution at the expense of counting sensitiv

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single 3 inch NaI probe, the output from which was recorded by a ratemeter and y-t recorder.

The patient was placed at rest in a quiet room with his head parallel to the gamma camera with modified collimator. The patient's brain base line (lateral canthus to external occipital protuberance) was positioned parallel to the lower holes of the collimator located such that these holes measured only brain activity (fig. 1). The contralateral cerebral hemisphere was monitored with a NaI detector placed at the mid-point of the calvarium, above the external auditory meatus. A nose clamp and a rubber mouthpiece, connected to the Ventil-con spirometer, were then placed into position.

The arterial xenon concentration was estimated from the end tidal values of the rebreathing curve. This was recorded by a second NaI detector placed over the airway adjacent to the patient's mouth. Care was taken to ensure that this detector was well shielded from activity arising from the patient. The count rate from this detector was also recorded on a y-t recorder. Data representing end tidal values were subsequently entered manually into the computer to allow correction for recirculating activity. Expired CO₂ concentration was continuously monitored to assess patient stability throughout the measurement.

When the patient was comfortable with stable pCO₂ and respiratory rate, rebreathing of ¹³³Xe at a concentration of 5 mCi · ℓ⁻¹ (185 MBq · ℓ⁻¹) commenced and continued for one minute. After this the spirometer was switched to open circuit and measurements continued for a further 9 minutes. At the commencement of rebreathing the ¹³³Xe, the cerebral activity, as measured by the gamma camera was stored by the PDP 11/40 computer as a series of six second frames. At the end of the study the counts were displayed on a colour monitor to enable regions of interest to be selected. Activity time curves were then analysed including correction for recirculating activity to enable r-CBF to be calculated. A similar analysis was performed for manually entered data from the NaI detector on the contralateral hemisphere.

Throughout the procedure, care was taken to ensure that the patient was not disturbed. It has been noted that patient arousal causes significant changes in cerebral blood flow.

**Theory**

The theoretical basis for the measurement of blood flow using inert, diffusible, radioactive tracers was originally described by Kety. Recirculation of arterial activity and the presence of three separate compartments in the brain representing grey matter, white matter and extracerebral tissue, respectively, complicate the simple exponential decay of activity so that the activity time curve is of the form

\[ C(t) = \sum_{i=1}^{3} W_i \lambda_i e^{-\lambda_i t} \int_0^t Ca(u) e^{\lambda_i u} du \]

Here \( W_i \) represents the relative mass of tissue; \( \lambda_i \) the blood tissue partition coefficient and \( \lambda_i k_i \) the blood flow per unit mass of tissue in the \( i \)th tissue compartment. \( Ca(t) \) is the arterial activity at time, \( t \).

Although such a three compartment model gives excellent fits to the data, it requires extremely accurate data to be collected over a period of 40 minutes. In view of these restrictions, only the single and two compartment models, using equation 1 with one and two components, have been considered.

To examine the advantages and disadvantages of both models a theoretical analysis was performed with data created using equation 1 and values for the parameters which were derived from the measurements of Obrist et al. The values chosen to represent a normal subject were:

- \( k_1 = 0.94 \)
- \( k_2 = 0.17 \)
- \( k_3 = 0.03 \)
- \( W_1 = 0.32 \)
- \( W_2 = 0.20 \)
- \( W_3 = 0.48 \)
- \( \lambda_1 = 0.8 \)
- \( \lambda_2 = 1.5 \)
- \( \lambda_3 = 1.0 \)

The assumption that \( \lambda_3 = 1.0 \) is not restrictive since only the product \( \lambda_3 W_3 \) enters the calculation.

Random statistical fluctuations with a standard deviation equal to the square root of each six second count were superimposed on data calculated using equation 1. The resulting set of data was then analysed by fitting equation 1 with either one or two terms to represent the single or two compartment models. Calculated constants for the two models are labelled with a superscript S or T to distinguish between them.

**Statistical Accuracy**

One of the most important considerations of any analysis technique is the accuracy of the calculated

*This latter curve fitting was performed using a program kindly provided by Dr. Obrist.*
parameters for a given statistical variation on the data. For a given maximum cerebral count rate the analysis was performed a number of times on sets of data which only differed in the random statistical noise added to the theoretical curve of equation 1 using a Monte Carlo technique. Poisson statistics were assumed, so that the standard deviation on a given six second count was taken to be the square root of that count. Between 11 and 13 such analyses were performed for a single peak count rate, and the mean value of parameters and their standard deviation were calculated. This was done for five different peak count rates. The analysis showed that the standard deviation (and hence the coefficient of variation) on the calculated value of \( k_1 \) depended on the square root of the peak count rate as would be expected. The coefficients of variation found for a variety of circumstances is displayed in table 1.

Table 1 shows the results of such a series of calculations for the two compartment model fitted from 1.5 to 10 minutes after commencing rebreathing and for the single compartment model fitted from 1.5 minutes for 1, 2 and 3 minutes respectively. It is evident that the accuracy of the value of \( k_1 \), determined by the single compartment model, depends very strongly on the period of data considered. With only one minute of data the accuracy attainable is not as good as that from the two compartment model. However, for analysis over longer periods of time, the accuracy of the single compartment model is greatly improved.

When 5 mCi • \( \cdot \) \( e^{-1} \) (185 MGq • \( \cdot \) \( e^{-1} \)) of xenon\(^{133} \) is rebreathed for a period of one minute it is found that the brain activity reaches a peak of approximately 150 counts sec\(^{-1} \) from a single brain region, as defined by the collimator. This value is significantly lower in cases of reduced blood flow in the brain. Thus, for a single brain region it is essential that the analysis be performed using the single compartment model with two or three minutes of data to achieve adequate statistical accuracy. It is generally possible to combine up to five regions on the camera if the total flow is required; this results in some improvement but still leaves the two compartment model with barely acceptable accuracy. For this reason the single compartment model is preferable in cases where a limited count rate is available. It is therefore particularly valuable where carotid injection is not acceptable.

Although the most accurate CBF is obtained by using the single compartment model fitted to several minutes of data, it is found that the effect of other compartments becomes more significant when the analysis is performed using data over a longer period of time. For most situations, a reasonable compromise is to confine the analysis to two minutes of data.

**Blood Flow Calculation**

The two compartment model yields two parameters which are designated by \( k_2 \) and \( k_3 \). These are related to the cerebral blood flow in the two compartments. Obrist\(^7 \) has shown that the first is almost equal to the constant \( k_1 \) representing grey matter flow in equation 1. The second is, however, a combination of the values of \( k_1 \) and \( k_2 \). Thus, to excellent accuracy, the grey matter blood flow per gram of tissue is given by 0.8 \( k_1 \), where 0.8 is the partition coefficient, \( \lambda_1 \), measured by Veall and Mallett.\(^9 \)

The single compartment model gives a single clearance parameter \( k_2 \), which is affected by the values of \( k_1 \), \( k_2 \) and \( k_3 \) in equation 1. Table 2 gives the effect on the calculated \( k_2 \) value of modifying the values of constants \( k_2 \) and \( k_3 \) from the values of 0.17 and 0.03, which were obtained by Obrist\(^7 \) on normal subjects. It can be seen from the table that variation of \( k_2 \) or \( k_3 \) has a relatively minor effect on the calculated value of \( k_2 \). The value of \( k_3 \) is chiefly affected by the value of \( k_1 \). Variation of \( k_2 \) shows that the single compartment clearance rate, \( k_1 \), is proportional to \( k_1 \) over a wide range of values. The proportionality constant has the value 0.57 for normal grey matter flow and 0.64 for flow rates which are 40% lower than normal. The correction factor 0.6 has been chosen as the best value to relate the measured slope (\( k_2 \)) to the actual value of \( k_1 \). Hence the grey matter blood flow per 100 g of tissue is approximately given by 133 \( k_2 \), where 1.33 arises from a combination of the partition coefficient of 0.8 and the correction factor of 0.6. Figure 2 shows a plot of theoretical grey matter flow against 133 \( k_2 \) for various values of \( k_1 \), ranging from 0.3 to 1.3. These results are unchanged if both \( k_1 \) and \( k_2 \) are varied simultaneously (keeping their ratio at 5.5) which may be more physiologically relevant.

Wyper et al\(^7 \) related their measured slope to the mean blood flow. However, since decreased values of \( k_2 \) cause an increase in slope (\( k_2 \)), whereas the mean

<table>
<thead>
<tr>
<th>TABLE 1 Statistical Accuracy — Monte Carlo Calculation*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single compartment model</strong></td>
</tr>
<tr>
<td>Fitted 1.5–2.5 min</td>
</tr>
<tr>
<td>Fitted 1.5–3.5 min</td>
</tr>
<tr>
<td>Fitted 1.5–4.5 min</td>
</tr>
</tbody>
</table>

| **Two compartment model** | **Coefficient of variation in \( k_2 \) for peak count C** | **Counts in peak for 5% coefficient of variation** |
| Fitted 1.5–10 min | 265/√C | 2800 |

*1 min rebreathing — 6 sec counts — normal flow.

<table>
<thead>
<tr>
<th>TABLE 2 Single Compartment Model: Measured Slope ( k_2 ) with Changing ( k_2 ) and ( k_3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measured Slope ( k_2 )</strong></td>
</tr>
<tr>
<td><strong>Value of ( k_3 ) or ( k_3 )</strong></td>
</tr>
<tr>
<td>40% below normal*</td>
</tr>
<tr>
<td>Normal*</td>
</tr>
<tr>
<td>50% above normal*</td>
</tr>
<tr>
<td>Range of blood flow</td>
</tr>
</tbody>
</table>

*The table gives values of \( k_2 \) when \( k_3 \) and \( k_3 \) are below, equal to or above the values 0.17 and 0.03 found for normal subjects.
Results

As a result of the above analysis, all patient results have been analysed using a single compartment model fitted from 0.5 to 2.5 minutes after rebreathing has ceased. The grey matter flow has been taken to be $133 k_s \text{ ml} \cdot \text{minute}^{-1} \cdot 100 \text{ g brain}^{-1}$.

Normal Population

Twelve normal volunteers (eight males and four females) with no known disease at the time of measurement were measured to establish a normal range. The mean hemispheric CBF was $64.6 \pm 10 \text{ ml} \cdot \text{minute}^{-1} \cdot 100 \text{ g brain}^{-1}$. There was no statistically significant difference between right and left hemispheres. Frontal region r-CBF is slightly higher than posterior region r-CBF but is not statistically significant (table 4).

Comparison of First and Retest Measurements

Sixty-one patients, who were investigated for sub-arachnoid haemorrhage, cerebrovascular disease or dementia, were retested sixty minutes after their initial r-CBF. The mean CBF in the first measurement was $47.5 \pm 9.4 \text{ ml} \cdot \text{minute}^{-1} \cdot 100 \text{ g brain}^{-1}$ and that in the second measurement was $46.8 \pm 9.0 \text{ ml} \cdot \text{minute}^{-1} \cdot 100 \text{ g brain}^{-1}$. There is no statistical difference between the test and the retest measurements. The two measurements showed good reproducibility represented by a coefficient of variation of 6.5%; they are graphically represented in figure 4.

The observed variation between first and second

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Single Compartment Model Measured Slope $k_s$ with Changing Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured Slope $k_s$</td>
<td>$W_1/W_2$ &amp; $W_3/W_2$ varying</td>
</tr>
<tr>
<td>Ratio of weights</td>
<td>$0.45$</td>
</tr>
<tr>
<td>$40%$ below normal*</td>
<td>$0.52$</td>
</tr>
<tr>
<td>Normal*</td>
<td>$0.60$</td>
</tr>
<tr>
<td>$50%$ above normal*</td>
<td>$\pm 14%$</td>
</tr>
</tbody>
</table>
| Range of blood flow | *The table gives values of $k_s$ when the ratio of any two weights is below, equal to or above the values found for normal subjects.
measuring appears to be due to physiological factors since a variation of only 2.5% would be expected from the observed maximum six second count using the results of table 1. This is confirmed by comparison of different regions of the brain in successive measurements where the variation agrees with that expected statistically.

Clinical Results

Subarachnoid Haemorrhage

Forty-six patients with proven subarachnoid haemorrhage (SAH) secondary to a cerebral aneurysm had CBF measured within the first seven days after their ictus while they were clinically grade 1 or 2 according to the Botterell classification. The patients were monitored daily for evidence of cerebral ischaemia. This was judged clinically by gradual neurological deterioration without evidence of rebleeding or hydrocephalus as assessed by a CT scan.

Fifteen patients (32%) subsequently developed clinical evidence of cerebral ischaemia. The mean initial CBF of this subgroup of patients was 42 ± 6 ml • minute^-1 • 100 g brain^-1, while patients without clinical evidence of cerebral ischaemia had an initial mean CBF of 49 ± 11 ml • minute^-1 • 100 g brain^-1. These differences are statistically significant as shown by a two sample t-test and both are significantly different from our control population.

Thirty-five patients had two or more serial CBF measurements, of whom 13 showed a significant (greater than 20%) reduction in their blood flow after the initial measurement. Of these, 6 subsequently developed cerebral ischaemia. Three of the remaining 22 patients developed cerebral ischaemia, but one of whom had an initial blood flow less than 50 ml minute^-1 • 100 g brain^-1.

The observation that decreasing cerebral blood flow frequently precedes clinically evident ischaemia is illustrated by the following case report: A 51 year old woman was admitted following a sudden onset of headache. She was confused, irritable and had marked neck stiffness. The only focal neurological sign was an upgoing right plantar.

Computed tomography (CT) confirmed a SAH. Within 24 hours she had improved, and was orientated with no focal signs. CBF forty-eight hours after her SAH was 48 ml • minute^-1 • 100 g brain^-1 (right) and 47 ml • minute^-1 • 100 g brain^-1 (left). She remained neurologically stable until the seventh day after her SAH when she again became confused and developed a right hemiparesis. CBF on the eighth day was 33 ml • minute^-1 • 100 g brain^-1 (right) and 35 ml • minute^-1 • 100 g brain^-1 (left), a 33% reduction in CBF. Her clinical deterioration was attributed to cerebral vasospasm as there was no evidence of rebleeding or hydrocephalus on a repeat CT scan. The neurological deficit maximized by the ninth day, after which she made a steady improvement. Twenty-two days after the SAH her neurological signs had resolved and CBF was 47 ml • minute^-1 • 100 g brain^-1 in both hemispheres. Angiography was then performed and a pericallosal aneurysm was demonstrated. There was no angiographic evidence of vasospasm. The patient was operated upon 24 days after the SAH without post-operative complications.

Transient Cerebral Ischaemia

Seventeen patients who had recovered neuropsychologically from a transient cerebral ischaemia episode, were assessed by CBF measurement. The mean CBF of all patients was 51 ± 6 ml • minute^-1 • 100 g brain^-1 which is significantly lower than that of our control population. Of eight patients receiving cerebral angiography, three had unilateral stenosis or carotid bifurcation plaque with a mean flow of 55 ml • minute^-1 • 100 g brain^-1 and five had bilateral carotid stenosis with a mean flow of 50.6 ml • minute^-1 • 100 g brain^-1.

Discussion

A number of authors have obtained good results using a gamma camera in combination with intra-carotid injection to measure regional cerebral blood flow. However in combination with xenon inhalation the use of the gamma camera has not been widely accepted. Podreka9 has recently reported a comparison of the intravenous injection of xenon and the intra-carotid technique using a modified collimator and the gamma camera with good results. Klassen10 used the gamma camera and inhalation of xenon but was only able to measure average hemispheric flow.

The collimator described in this paper gives a greatly improved count rate over a conventional collimator while still enabling regional blood flow to be measured if desired.

Further to this, examination of analysis techniques has shown that a single compartment model using two minutes of data can achieve the same statistical accuracy as a two compartment model using data with six times the count rate. The measured exponential slope is approximately proportional to the grey matter flow although it is also affected somewhat by activity in white matter and extracerebral compartments. The largest effects arise due to variations in the tissue com-
partment weighting factors. These are unlikely to change between measurements on a given patient, although considerable variation between normals has been observed. Thus sequential measurements of $K^\text{r}_2$ will reflect changes in cerebral blood flow, so that although the absolute precision of blood flow measurements using the single compartment model may be subject to error, the reproducibility for a given patient should be excellent.

Repeat measurements on patients showed a variability which cannot be readily attributed to statistical variations or inaccuracies in the analysis. Substantial blood flow changes have been observed when a patient is suddenly aroused from a state of relaxation and it is likely that the observed variation is due to physiological factors. Thus it is essential to ensure that patients are completely relaxed throughout the measurement if reproducible results are to be achieved.

Apart from improvement in statistical accuracy the single compartment analysis has the further advantage that blood flow measurements can be performed in 3½ minutes. This greatly facilitates measurements particularly on uncooperative or seriously ill patients.

Thus the combination of modified collimator design and simplified analysis enables statistically accurate and reproducible blood flow measurements to be made in any Nuclear Medicine Department which possesses a gamma camera-computer facility.

We have mainly applied the method to patients suffering from subarachnoid haemorrhage. Our data is in accord with the observations of others that CBF is significantly decreased in SAH.12-15 These studies have shown a serial reduction of CBF from Grade I to Grade IV patients which corresponds to the decreasing conscious state of patients in poor clinical grades. Our findings that patients of good clinical grade following SAH have a global reduction of CBF is in agreement with most other authors except Ferguson.16

Cerebral vasospasm occurs in 30% of patients of good clinical grade following a subarachnoid haemorrhage, and of these 60% will progress to permanent neurological deficit or death.17 Many surgeons agree that operating upon patients with cerebral vasospasm will aggravate the existing vasospasm and result in cerebral infarction that may not have occurred if the patient had been treated conservatively until this critical period had passed. To detect vasospasm, cerebral angiography is often performed and surgery delayed if vasospasm is demonstrated. Cerebral angiography, however, is an invasive procedure and associated with an increased mortality in patients following a subarachnoid haemorrhage.

We believe CBF measurement is a useful and safe adjunct to detecting cerebral vasospasm. Our results show that patients who develop cerebral ischaemia have a lower initial CBF than those who do not, even though both groups are clinically similar when initially assessed. Similarly Nilsson19 found 12 of 207 patients with a subarachnoid haemorrhage changed their clinical grade secondary to cerebral vasospasm and showed an increase in cerebral transit time. We confirm the findings of Weir14 and Voldby and Jensen20 concerning the usefulness of serial r-CBF in detecting cerebral vasospasm and its application in the overall management of patients following a subarachnoid haemorrhage.

Acknowledgments

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